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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,328	10/16/2003	Jose F. Arena	7230-8	8505

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EXAMINER
SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,328	ARENA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 1-10 in part, with a further election of 4959C>T in the reply filed on 10/30/06 is acknowledged. The traversal is on the ground(s) that that it would not pose an undue burden on the examiner to consider all of the polymorphisms together. This is not found persuasive because applicant's arguments center on the fact that "a search of early onset breast cancer mutations would reveal, if any, literature pertaining to any one of the…groups." However, this is not persuasive because the examination of the pending claims requires the search of all literature related to BRCA1 or BRCA2 mutations, and for each different mutation the search would be different, requiring the consideration of different genes or portions of the genome, using different key words and different nucleotide sequence searches. Furthermore, there are thousands of different references related to breast cancer mutations in BRCA1 alone, but even more when both BRCA1 and BRCA2 are considered. Applicant is reminded that if a claim to the elected group wherein the mutation is 5217A>G in BRCA1 is found to be allowable, the further restriction with regard to claim 2 will be withdrawn and all groups which include the elected polymorphism will be rejoined.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

2. The information disclosure statement filed 1/5/04 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the final listed reference is not a proper citation. The reference refers to a print out of a webpage, but the citation does not include date of the reference. The listing on the 1449 implies that the entire Mutation Data Base was provided for

consideration but only a two page cover page print out was provided. The reference has been lined through on the 1449. All other references were considered and were initialed. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objections

3. Claim 1 is objected to because of the following informalities: the recitation (5217G>A) appears to be a typographical error. The claim previously sets forth that this is an adenine to guanine transition which would be represented 5217A>G. This genetic alteration is also referred to throughout the specification as 5217A>G. Applicant's designation of the opposite in claim 1 thus appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-7 and 9-10 rejected under 35 U.S.C. 102(b) as being anticipated by Panguluri et al. (Human Genetics (1999) 105:28-31; provided in IDS).

Panguluri et al. teach a method for analyzing a biological sample comprising (a) obtaining a biological sample from a subject; and (b) analyzing the sample for the presence of a genetic polymorphism or mutation that is an adenine to guanine transition at position 5217 in the BRCA1 gene. Namely, Panguluri et al. teach analysis of the entire coding region of the BRCA1 gene from 45 African American breast cancer patients (p. 28). Thus, every single position within the entire coding region of the gene was analyzed for the presence of a genetic polymorphism or mutation, including position 5217 which is part of the coding sequence. The instant claims do not require that a particular variant sequence be detected, only that the sample is analyzed for the presence of the polymorphism or mutation. Since Panguluri et al. analyzed the entire coding region for any irregularities that were present, the teachings of Panguluri et al. anticipate the claim.

Regarding claim 2, position 4959 was also analyzed since it is also part of the coding sequence.

Regarding claim 3, the 943ins10 alteration was tested for and detected (Table 2).

The sample used by Panguluri et al. was blood (p. 29).

Panguluri et al. conduct a polymerase chain reaction step as part of the analyzing the sample (p. 29). Panguluri et al. amplify nucleic acids comprising all of the exons, including position 5217 of the BRCA1 gene (p. 29).

Panguluri et al. determine the nucleotide sequence of the genetic polymorphism or mutation by inference, the fact that no variant was detected at a particular position is informative that the "wild" type is present.

Panguluri et al. analyze all of the exons by single strand conformation polymorphism analysis (p. 29).

Panguluri et al. analyze DNA of subjects that are of African descent (p. 29).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Panguluri et al. in view of Livak et al (US Patent 5538848).

Panguluri et al. teach a method for analyzing a biological sample comprising (a) obtaining a biological sample from a subject; and (b) analyzing the sample for the presence of a genetic polymorphism or mutation that is an adenine to guanine transition at position 5217 in the BRCA1 gene. Namely, Panguluri et al. teach analysis of the entire coding region of the BRCA1 gene from 45 African American breast cancer patients (p. 28). Thus, every single position within

the entire coding region of the gene was analyzed for the presence of a genetic polymorphism or mutation, including position 5217 which is part of the coding sequence. The instant claims do not require that a particular variant sequence be detected, only that the sample is analyzed for the presence of the polymorphism or mutation. Since Panguluri et al. analyzed the entire coding region for any irregularities that were present; the teachings of Panguluri et al. anticipate the claim. Panguluri et al. conduct a polymerase chain reaction step as part of the analyzing the sample (p. 29). Panguluri et al. amplify nucleic acids comprising all of the exons, including position 5217 of the BRCA1 gene (p. 29).

Panguluri et al. do not conduct a real-time PCR amplification.

Livak et al. teach real time PCR methods and teach that an advantage of using such a method is the ability to know whether PCR is occurring while the cycling reactions are taking place, minimizing possible cross-contamination, and monitoring the efficiency of amplification reaction to be evaluated, which can indicate where reaction inhibitors are present in the sample (Col. 1, lines 30-52).

Thus, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by Panguluri et al. so as to have used the real-time PCR methods taught by Livak et al. One would have been motivated to use the real time PCR methods taught by Livak et al. in place of the conventional PCR taught by Panguluri et al. in order to have provided a means for monitoring the PCR progression while the reaction was taking place, in order to monitor for the presence of inhibitors, for example. In view of the teachings of the prior art, the claimed invention is prima facie obvious.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention concerns a method for analyzing a biological sample for the presence of a genetic polymorphism or mutation, namely the elected 5217A>G transition within the BRCA1 gene. The specification teaches that the method is useful "for evaluating the risk of breast cancer development in AA women (p. 2, lines 2-3)." Thus, the use of the claimed invention requires the knowledge of an association between the nucleotide present at position 5217 in the BRCA1 gene and the risk of breast cancer development.

The instant specification teaches that the 5217A>G transition was identified in African American (AA) women (p. 6, lines 20-21). The specification teaches that the transition results in a change from threonine to alanine at position 1700 of the encoded BRCA1 polypeptide. The specification does not provide any data to establish that this polymorphism is predictive of breast cancer in African American women or in any women or man. The specification teaches that the polymorphism was identified in AA women, but does not teach that the women it was identified in actually were breast cancer patients. There are no working examples in the specification

where the claimed method was used to successfully predict the risk of developing breast cancer in a subject.

At the time the invention was made, the human BRCA1 gene was known, as noted by the specification, as well as many different mutations and polymorphisms within the gene. Some of these were known to be associated with the risk of developing breast cancer. The instantly disclosed polymorphism, whose analysis is the subject of the claimed methods appears to be first disclosed in this patent application. Thus, the prior art is silent as to the functionality or effect of this polymorphism. It was highly unpredictable at the time the invention was made as to which of the many different known alterations in the BRCA1 gene were predictive of breast cancer, in women or men, no matter what ethnic background. Newman et al. (1998, as cited in the IDS) teach, "testing for cancer predisposition due to inherited BRCA1 mutation is complicated by limited information about frequency of BRCA1 mutations in the general population. In the human BRCA1 gene, more than 100 distinct variants have been reported. Of those variants that are disease related, nearly all are frameshift or nonsense mutations leading to truncated proteins (p. 916, 1st column)." Indeed, the post-filing date art continues to reiterate the unpredictable nature of this technology area. Judkins et al. (Mutation Research, 2005, Vol. 573, pages 168-179) teach that even so far after the instant invention "it has proven difficult to characterize the clinical significance of genetic variants that do not obviously truncate the open reading frames of genes. These genetic variants of uncertain clinical significance diminish the value of genetic test results (Abstract)." The 5217A>G transition is neither a truncation nor a frame shift mutation.

Phelan et al. include the P1614S and T1700A mutations in a group of germline missense mutations whose function was unknown as of the writing of their paper in 2006 (Phelan et al.

Journal of Medical Genetics, 2005, Volume 42, pages 138-146; p. 139). Phelan et al. further discuss the elusive nature of the determination of the clinical relevance of missense variants. Phelan et al. discuss the extensive experimentation that is necessary to consider in the classification of a BRCA1 variant as deleterious or high risk, including the rate of occurrence in high risk individuals versus controls, the segregation of the variant in family members affected by the disease, sequence comparisons, and functional analysis (p. 143). Any single one of these avenues useful for characterizing the functionality of a variant requires extensive work which itself is highly unpredictable. For example, Phelan et al. teach that allele "frequencies differ considerably between ethnic groups." Thus, for the instant claims to be practiced to their full scope, one would have to determine that the 5217A>G transition occurs in non-AA subjects, and even within the AA population one would have to undertake extensive experimentation and data gathering to determine if this alteration has any clinical relevance.

Thus, having carefully considered the nature of the invention, he teachings in the specification, the lack of working examples relative to the 5217A>G alteration in the BRCA1 gene, the highly unpredictable nature of the art area, and the extensive experimentation necessary to discover if the 5217A>G alteration in the BRCA1 gene is predictive of a breast cancer phenotype in AA women, let alone any other ethnic groups of women or men, it is concluded that it would require undue experimentation to use the claimed invention. There can be no doubt that one would be able to follow the guidance in the prior art and the specification to actually screen for the allele present at the 5217 position of the human BRCA1 gene, however, this rejection is written to address the "use" portion of 112 1st paragraph. The specification teaches

only one use for the claimed invention, and after careful consideration of all of these factors, it is evident that it would require undue experimentation to use the claimed invention.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of

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Juliet C. Switzer
Primary Examiner
Art Unit 1634

January 4, 2007